

FILE 'HOME' ENTERED AT 08:27:26 ON 22 MAY 2003)

FILE 'MEDLINE, EMBASE, CAPLUS' ENTERED AT 08:28:17 ON 22 MAY 2003

L1	0 S	PROTEASE (A) VON WILEBRAND FACTOR
L2	7 S	VON WILEBRAND FACTOR
L3	0 S	L2 (A) PROTEASE
L4	0 S	L2(A) CLEAVING
L5	85 S	VWF (A) PROTEASE
L6	42	DUPLICATE REMOVE L5 (43 DUPLICATES REMOVED)

FILE 'USPATFULL, EUROPATFULL, JAPIO, PATOSWO' ENTERED AT 08:56:21 ON 22 MAY 2003

L7	0 S	L6
L8	3 S	PROTEASE (A) VWF

6 ANSWER 37 OF 42 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 25
 AN 2001022649 EMBASE
 TI A rapid assay for the **vWF protease**.
 AU Aronson D.L.; Krizek D.M.; Rick M.E.
 CS Dr. M.E. Rick, Hematology Service, Clinical Center, National Institutes
 of Health, 10 Center Drive, Bethesda, MD 20892, United States.
 mrick@cc.nih.gov
 SO Thrombosis and Haemostasis, (2001) 85/1 (184-185).
 Refs: 4
 ISSN: 0340-6245 CODEN: THHADQ
 CY Germany
 DT Journal; Letter
 FS 029 Clinical Biochemistry
 025 Hematology
 LA English
 CT Medical Descriptors:
 *thrombotic thrombocytopenic purpura: DI, diagnosis
 *enzyme assay
 human
 protein degradation
 quantitative assay
 letter
 priority journal
 Drug Descriptors:
 *von Willebrand factor: EC, endogenous compound
 *proteinase: EC, endogenous compound
 collagen
 RN (von Willebrand factor) 109319-16-6; (proteinase) 9001-92-7; (collagen)
 9007-34-5

6 ANSWER 32 OF 42 CAPLUS COPYRIGHT 2003 ACS

AN 2002:19229 CAPLUS

DN 136:399299

TI Aetiology and pathogenesis of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: The role of von willebrand factor-cleaving protease

AU Furlan, Miha; Laemmle, Bernhard

CS Central Hematology Laboratory, Inselspital, University Hospital, Bern, Switz.

SO Best Practice & Research, Clinical Haematology (2001), 14(2), 437-454
CODEN: BPRCA5

PB Bailliere Tindall

DT Journal; General Review

LA English

CC 14-0 (Mammalian Pathological Biochemistry)

AB A review. Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are today often regarded as variants of one syndrome denoted as TTP/HUS, characterized by thrombocytopenia caused by intravascular platelet clumping, microangiopathic hemolytic anemia,

fever, renal abnormalities and neurol. disturbances. Unusually large von Willebrand factor multimers have been obsd. in plasma from patients with chronic relapsing forms of TTP. Their appearance in patients with classic

TTP is caused by deficiency of a specific von Willebrand factor-cleaving protease. A constitutional deficiency of this protease has consistently been found in familial cases of TTP, whereas in acquired TTP the protease deficiency is caused by the presence of an inhibiting autoantibody. A normal activity of von Willebrand factor-cleaving protease was

established in patients with HUS. In this chapter, the authors report 23 cases with severe constitutional protease deficiency: about 1/2 of these patients

had their first acute episode as children, whereas the other half had their first TTP event at an adult age, several of them during their first pregnancy. 2 Of these 23 individuals with congenital protease

deficiency, both older than 35 yr, have never had an acute TTP event. These results indicate that a deficiency of von Willebrand factor-cleaving protease alone is not sufficient to cause acute TTP. Patients with long-lasting dormant protease deficiency were found to experience multiple relapses of TTP after having had their first acute episode. In 1 protease-deficient, plasma-dependent patient with chronic relapsing TTP, the authors estd. that 5% of normal protease activity is sufficient to remove the most adhesive von Willebrand factor multimers and prevent the formation of platelet microthrombi. The deficiency of von Willebrand factor-cleaving protease is a very strong risk factor for TTP, but the development of an acute bout requires a trigger, possibly causing the activation or apoptosis of endothelial cells in the microcirculation. It is unclear whether anti-endothelial cell antibodies, cytokines or other agents are involved in triggering thrombotic microangiopathy. The release of platelet calpain (and/or other proteases), leading to a degrdn. of von Willebrand factor and to platelet aggregation, was reported in patients during their acute TTP episode. It is unknown whether calpain directly triggers an acute event or whether it merely reflects its release during the aggregation of platelets by the unusually large von Willebrand factor multimers. With regard to the heterogeneous etiol. of thrombotic microangiopathies, requiring distinct therapeutic measures, a new classification of thrombotic microangiopathy should replace the current, frequently inappropriate clin. discrimination between TTP and hemolytic

uremic syndrome.
ST review human von Willebrand disease 2 **vWF protease**
deficiency; calpain **vWF protease** deficiency von
Willebrand disease human review; autoantibody **vWF**
protease deficiency von Willebrand disease human review

L6 ANSWER 31 OF 42 MEDLINE DUPLICATE 23
 AN 2001558966 MEDLINE
 DN 21230281 PubMed ID: 11332762
 TI Clinical application of a rapid method using agarose gel electrophoresis and Western blotting to evaluate von Willebrand factor protease activity.
 AU Kirzek D M; Rick M E
 CS Warren Grant Magnuson Clinical Center, National Institutes of Health, Bethesda, MD 20892, USA.
 SO ELECTROPHORESIS, (2001 Mar) 22 (5) 946-9.
 Journal code: 8204476. ISSN: 0173-0835.
 CY Germany: Germany, Federal Republic of
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Priority Journals
 EM 200110
 ED Entered STN: 20011022
 Last Updated on STN: 20011022
 Entered Medline: 20011018
 AB A method for evaluating the activity of the von Willebrand factor (**vWF**) **protease** is described, and a clinical application is illustrated. The procedure utilizes gel electrophoresis, Western blotting, and luminographic detection methods to evaluate the distribution of vWF multimers before and after incubation of clinical samples under conditions that favor proteolysis by this enzyme. Physiologically, the high-molecular-weight multimers of vWF are cleaved by the **vWF protease** under conditions of high shear stress in parts of the arterial circulation; cleavage of vWF multimers is also observed after exposure of vWF to denaturing agents in vitro and thus can serve as a laboratory test for the activity of the **protease**. **vWF protease** activity is decreased or absent in patients with thrombotic thrombocytopenic purpura due to an inhibiting autoantibody, and this leads to high levels of noncleaved vWF and to life-threatening thrombosis, thrombocytopenia and anemia. The assay evaluates the activity of the protease by assessing the cleavage of vWF multimers after patient plasmas are incubated in vitro under denaturing conditions. With the use of these electrophoresis and Western blotting techniques, patient plasmas can be rapidly assessed for the activity of the **vWF protease** which may aid in the treatment strategy for these

6 ANSWER 27 OF 42 MEDLINE DUPLICATE 20

AN 2001492843 MEDLINE

DN 21426500 PubMed ID: 11535494

TI Partial amino acid sequence of purified von Willebrand factor-cleaving protease.

AU Gerritsen H E; Robles R; Lammle B; Furlan M

CS Central Hematology Laboratory, University Hospital, Inselspital, Bern, Switzerland.

SO BLOOD, (2001 Sep 15) 98 (6) 1654-61.
Journal code: 7603509. ISSN: 0006-4971.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200110

ED Entered STN: 20010906
Last Updated on STN: 20011015
Entered Medline: 20011011

AB von Willebrand factor-cleaving **protease** (vWF-cp) is responsible for the continuous degradation of plasma vWF multimers released from endothelial cells. It is deficient in patients with thrombotic thrombocytopenic purpura, who show unusually large vWF multimers in plasma. Purified vWF-cp may be useful for replacement in these patients, who are now treated by plasma therapy. In this study, vWF-cp was purified from normal human plasma by affinity chromatography on the IgG fraction from a patient with autoantibodies to vWF-cp and by a series of further chromatographic procedures, including affinity chromatography on Protein G, Ig-TheraSorb, lentil lectin, and heparin. Four single-chain protein bands, separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis under nonreducing conditions, showed M(r) of 150, 140, 130, and 110 kd and were found to share the same N-terminal amino acid sequence, suggesting that they were derived from the same polypeptide chain that had been partially degraded at the carboxy-terminal end. A hydrophobic sequence (Ala-Ala-Gly-Gly-Ile-Leu-His-Leu-Glu-Leu-Leu-Val-Ala-Val-Gly) of the first 15 residues was established. The protease migrates in gel filtration as a high-molecular-weight complex with clusterin, a 70-kd protein with chaperonelike activity. vWF-cp bound to clusterin is dissociated by the use of concentrated chaotropic salts. vWF-cp in normal human plasma or serum is not associated with clusterin, suggesting that the observed complex is due to vWF-cp denaturation during the purification procedure. Activity of vWF-cp is unusually stable during incubation at 37 degrees C; its in vitro half-life in citrated human plasma, heparin plasma, or serum is longer than 1 week. There was even a temporary increase in protease activity during the first 3 days of incubation.

6 ANSWER 23 OF 42 MEDLINE
 AN 2001321536 MEDLINE
 DN 21072606 PubMed ID: 11204576
 TI A rapid assay for the **vWF protease**.
 AU Aronson D L; Krizek D M; Rick M E
 SO THROMBOSIS AND HAEMOSTASIS, (2001 Jan) 85 (1) 184-5.
 Journal code: 7608063. ISSN: 0340-6245.
 CY Germany: Germany, Federal Republic of
 DT Letter
 LA English
 FS Priority Journals
 EM 200106
 ED Entered STN: 20010611
 Last Updated on STN: 20010611
 Entered Medline: 20010607
 CT Check Tags: Human
 *Clinical Chemistry Tests: MT, methods
 Collagen: ME, metabolism
 *Metalloendopeptidases: AN, analysis
 Metalloendopeptidases: BL, blood
 Purpura, Thrombotic Thrombocytopenic: BL, blood
 Purpura, Thrombotic Thrombocytopenic: DI, diagnosis
 Time Factors
 RN 9007-34-5 (Collagen)
 CN EC 3.4.24 (Metalloendopeptidases); EC 3.4.24.- (von Willebrand
 factor-degrading protease)

6 ANSWER 22 OF 42 MEDLINE DUPLICATE 17

AN 2002111690 MEDLINE

DN 21831815 PubMed ID: 11843286

TI Von Willebrand factor-cleaving protease and Upshaw-Schulman syndrome.

AU Fujimura Yoshihiro; Matsumoto Masanori; Yagi Hideo; Yoshioka Akira; Matsui Taei; Titani Koiti

CS Department of Blood Transfusion Medicine, Nara Medical University, Kashihara City, Japan.. yfujimur@nmu-gw.cc.naramed-u.ac.jp

SO INTERNATIONAL JOURNAL OF HEMATOLOGY, (2002 Jan) 75 (1) 25-34. Ref: 102
Journal code: 9111627. ISSN: 0925-5710.

CY Ireland

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)

LA English

FS Priority Journals

EM 200204

ED Entered STN: 20020215
Last Updated on STN: 20020424
Entered Medline: 20020423

AB Vascular endothelial cell (EC)-produced plasma von Willebrand factor (vWF) plays a critical role in primary hemostasis through its action of anchoring platelets onto the injured denuded subendothelial matrices under high shear stress. Unusually large vWF multimers (UL-vWFMs), present in plasma immediately after release from ECs, are most biologically active, but they are soon cleaved and degraded into smaller vWFMs by a specific plasma protease, termed vWF-cleaving **protease (vWF-CPase)**, in normal circulation. Recent studies on the relationship between UL-vWFMs and vWF-CPase, together with its autoantibody (inhibitor) have brought about a clear discrimination between thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Furthermore, a congenital deficiency of this enzyme activity has been shown to cause Upshaw-Schulman syndrome, a complex constitutional bleeding diathesis. Successful purification of vWF-CPase revealed that this enzyme is composed of a single polypeptide with a molecular mass of approximately 190 kd, and its complementary DNA cloning unambiguously indicated that it is uniquely produced in the liver and its gene is located on chromosome 9q34. The messenger RNA of vWF-CPase had a span of 4.6 kb, and its enzyme was designated ADAMTS 13. The predicted complete amino acid sequence of this enzyme consisted of 1427 residues, including a signal peptide, a short propeptide terminating in the sequence RQRR, a reprotolysin-like metalloprotease domain, a disintegrin-like domain, a thrombospondin-1 repeat (TSP1), a cysteine-rich domain, an ADAMTS spacer, 7 additional repeats, and 2 CUB domains.

TSP1

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov'

L6 ANSWER 12 OF 42 MEDLINE DUPLICATE 9
 AN 2002652564 MEDLINE
 DN 22299558 PubMed ID: 12393399
 TI Cloning, expression, and functional characterization of the von Willebrand factor-cleaving protease (ADAMTS13).
 AU Plaimauer Barbara; Zimmermann Klaus; Volkel Dirk; Antoine Gerhard; Kerschbaumer Randolph; Jenab Pegah; Furlan Miha; Gerritsen Helen; Lammle Bernhard; Schwarz Hans Peter; Scheifflinger Friedrich
 CS Baxter BioScience, Biomedical Research Center, Orth, Austria.
 SO BLOOD, (2002 Nov 15) 100 (10) 3626-32.
 Journal code: 7603509. ISSN: 0006-4971.
 CY United States
 DT Journal; Article; (JOURNAL ARTICLE)
 LA English
 FS Abridged Index Medicus Journals; Priority Journals
 EM 200303
 ED Entered STN: 20021105
 Last Updated on STN: 20030311
 Entered Medline: 20030310
 AB Deficient von Willebrand factor (VWF) degradation has been associated with thrombotic thrombocytopenic purpura (TTP). In hereditary TTP, the specific VWF-cleaving **protease** (VWF-cp) is absent or functionally defective, whereas in the nonfamilial, acquired form of TTP, an autoantibody inhibiting VWF-cp activity is found transiently in most patients. The gene encoding for VWF-cp has recently been identified as a member of the metalloprotease family and designated ADAMTS13, but the functional activity of the ADAMTS13 gene product has not been verified. To establish the functional activity of recombinant VWF-cp, we cloned the complete cDNA sequence in a eukaryotic expression vector and transiently expressed the encoded recombinant ADAMTS13 in HEK 293 cells. The expressed protein degraded VWF multimers and proteolytically cleaved VWF to the same fragments as those generated by plasma VWF-cp. Furthermore, recombinant ADAMTS13-mediated degradation of VWF multimers was entirely inhibited in the presence of plasma from a patient with acquired TTP. These data show that ADAMTS13 is responsible for the physiologic proteolytic degradation of VWF multimers.
 CT Check Tags: Human

6 ANSWER 11 OF 42 MEDLINE DUPLICATE 8

AN 2002464953 MEDLINE

DN 22199835 PubMed ID: 12181489

TI Mutations and common polymorphisms in ADAMTS13 gene responsible for von Willebrand factor-cleaving protease activity.

CM Comment in: Proc Natl Acad Sci U S A. 2002 Sep 3;99(18):11552-4

AU Kokame Koichi; Matsumoto Masanori; Soejima Kenji; Yagi Hideo; Ishizashi Hiromichi; Funato Masahisa; Tamai Hiroshi; Konno Mutsuko; Kamide Kei; Kawano Yuhei; Miyata Toshiyuki; Fujimura Yoshihiro

CS Research Institute, National Cardiovascular Center, Suita, Osaka 565-8565, Japan.

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (2002 Sep 3) 99 (18) 11902-7.
Journal code: 7505876. ISSN: 0027-8424.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 200209

ED Entered STN: 20020913
Last Updated on STN: 20030105
Entered Medline: 20020927

AB von Willebrand factor (VWF) is synthesized primarily in vascular endothelial cells and secreted into the plasma as unusually large VWF multimers. Normally, these multimers are quickly degraded into smaller forms by a plasma metalloproteinase, VWF-cleaving **protease** (VWF-CP). Decreases in the activity of this enzyme result in congenital and acquired thrombotic thrombocytopenic purpura (TTP). The human VWF-CP has recently been purified. Cloning of the corresponding cDNA revealed that the 1,427-aa polypeptide is a member of the ADAMTS gene family, termed ADAMTS13. Twelve rare mutations in this gene have been identified in patients with congenital TTP. Here, we report missense and nonsense mutations in two Japanese families with Upshaw-Schulman syndrome, congenital TTP with neonatal onset and frequent relapses. The comparison of individual ADAMTS13 genotypes and plasma VWF-CP activities indicated that the R268P, Q449stop, and C508Y mutations abrogated activity of the enzyme, whereas the P475S mutant retained low but significant activity. The effects of these mutations were further confirmed by expression analysis in HeLa cells. Recombinant VWF-CP containing either the R268P or C508Y mutations was not secreted from cells. In contrast, Q449stop and P475S mutants were normally secreted but demonstrated minimal activity. Genotype analysis of 364 Japanese subjects revealed that P475S is heterozygous in 9.6% of individuals, suggesting that approximately 10% of the Japanese population possesses reduced VWF-CP activity. We report on a single-nucleotide polymorphism associated with alterations in VWF-CP activity; it will be important to assess this single-nucleotide polymorphism as a risk factor for thrombotic disorders.

6 ANSWER 9 OF 42 CAPLUS COPYRIGHT 2003 ACS

AN 2002:408784 CAPLUS

DN 137:2413

TI Purification, cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease

IN Laemmle, Bernhard; Gerritsen, Helena Elisabeth; Furlan, Miha; Turecek, Peter; Schwarz, Hans-Peter; Scheifflinger, Friedrich; Antoine, Gerhard; Kerschbaumer, Randolph; Tagliavacca, Luigina; Zimmermann, Klaus; Voelkel, Dirk

PA Baxter Aktiengesellschaft, Austria

SO PCT Int. Appl., 93 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C12N009-64

ICS C12N015-57; C07K016-40; C12N005-10; G01N033-563; A61K038-48

CC 7-2 (Enzymes)

Section cross-reference(s): 1, 3, 13, 63

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002042441	A2	20020530	WO 2001-EP13391	20011120
	WO 2002042441	A3	20020808		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2002136713	A1	20020926	US 2001-833328	20010412
	AU 2002018306	A5	20020603	AU 2002-18306	20011120
PRAI	US 2000-721254	A	20001122		
	US 2001-833328	A	20010412		
	WO 2001-EP13391	W	20011120		
AB	The invention relates to a vWF cleaving protease (vWF				
	-cp) polypeptide, a cDNA mol. encoding the amino acid sequence of a				
vWF-cp	polypeptide and a compn. comprising the polypeptide. The invention also				
	relates to the use of the vWF cleaving protease polypeptide for prodn. of				
	vWF cleaving protease polypeptide binding mols. and for prodn. of a				
prepn.	for prophylaxis and therapy of thrombosis and thromboembolic disease.				
ST	von Willebrand factor protease human cDNA sequence; thrombosis				
	thromboembolic disease human von Willebrand factor protease				
IT	Purpura (disease)				
	(Henoch-Schoenlein's, prophylaxis and therapy of; purifn., cloning,				
	characterization and therapeutic use of human von Willebrand				
	factor-cleaving protease)				
IT	Cations				
	(divalent; purifn., cloning, characterization and therapeutic use of				
	human von Willebrand factor-cleaving protease)				
IT	Ligands				
	RL: BSU (Biological study, unclassified); NUU (Other use, unclassified);				
	BIOL (Biological study); USES (Uses)				
	(for affinity chromatog.; purifn., cloning, characterization and				
	therapeutic use of human von Willebrand factor-cleaving protease)				
IT	Gene, animal				

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (for von Willebrand factor-cleaving protease; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Immunoglobulins
 RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); NUU (Other use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (fragments, von Willebrand factor protease-binding; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Kidney, disease
 (hemolytic-uremic syndrome, prophylaxis and therapy of; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Chromosome
 (human 9, von Willebrand factor-cleaving protease mapping to; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Antibodies
 RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); NUU (Other use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (monoclonal, von Willebrand factor protease-binding; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Preeclampsia
 (prophylaxis and therapy of; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Anticoagulants
 Drug screening
 Genetic mapping
 Human
 Molecular cloning
 Phage display library
 Protein sequences
 cDNA sequences
 (purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Clusterin
 RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Antibodies
 RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified); NUU (Other use, unclassified); BIOL (Biological study); PREP (Preparation); USES (Uses)
 (single chain, von Willebrand factor protease-binding; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Platelet (blood)
 (thrombocytopenia, neonatal, prophylaxis and therapy of; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Embolism
 (thromboembolism, prophylaxis and therapy of; purifn., cloning, characterization and therapeutic use of human von Willebrand factor-cleaving protease)

IT Purpura (disease)
(thrombotic thrombocytopenic, prophylaxis and therapy of; purifn.,
cloning, characterization and therapeutic use of human von Willebrand
factor-cleaving protease)

IT Antibodies
Peptides, biological studies
Proteins
RL: BPN (Biosynthetic preparation); BUU (Biological use, unclassified);
NUU (Other use, unclassified); BIOL (Biological study); PREP
(Preparation); USES (Uses)
(von Willebrand factor protease-binding; purifn., cloning,
characterization and therapeutic use of human von Willebrand
factor-cleaving protease)

IT 431958-24-6P 431958-25-7DP, subfragments are claimed 431958-26-8P
RL: ANT (Analyte); BPN (Biosynthetic preparation); BSU (Biological study,
unclassified); PRP (Properties); PUR (Purification or recovery); THU
(Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP
(Preparation); USES (Uses)
(amino acid sequence; purifn., cloning, characterization and
therapeutic use of human von Willebrand factor-cleaving protease)

IT 431958-23-5
RL: ANT (Analyte); BSU (Biological study, unclassified); BUU (Biological
use, unclassified); NUU (Other use, unclassified); PRP (Properties); ANST
(Analytical study); BIOL (Biological study); USES (Uses)
(amino acid sequence; purifn., cloning, characterization and
therapeutic use of human von Willebrand factor-cleaving protease)

IT 78990-62-2, Calpain
RL: MSC (Miscellaneous)
(inhibitor, von Willebrand factor-cleaving protease activity in
presence of; purifn., cloning, characterization and therapeutic use of
human von Willebrand factor-cleaving protease)

IT 431958-27-9D, subfragments are claimed
RL: BSU (Biological study, unclassified); BUU (Biological use,
unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(nucleotide sequence; purifn., cloning, characterization and
therapeutic use of human von Willebrand factor-cleaving protease)

IT 334869-10-2P, Metalloprotease ADAMTS13 396097-95-3P, Proteinase,
metallo-, Von Willebrand factor, prepro-
RL: ANT (Analyte); BPN (Biosynthetic preparation); BSU (Biological study,
unclassified); PRP (Properties); PUR (Purification or recovery); THU
(Therapeutic use); ANST (Analytical study); BIOL (Biological study); PREP
(Preparation); USES (Uses)
(purifn., cloning, characterization and therapeutic use of human von
Willebrand factor-cleaving protease)

IT 431079-93-5 431079-94-6
RL: ANT (Analyte); BSU (Biological study, unclassified); BUU (Biological
use, unclassified); NUU (Other use, unclassified); PRP (Properties); ANST
(Analytical study); BIOL (Biological study); USES (Uses)
(purifn., cloning, characterization and therapeutic use of human von
Willebrand factor-cleaving protease)

IT 7439-95-4, Magnesium, biological studies 7440-24-6, Strontium,
biological studies 7440-39-3, Barium, biological studies 7440-70-2,
Calcium, biological studies
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(purifn., cloning, characterization and therapeutic use of human von
Willebrand factor-cleaving protease)

IT 431963-60-9 431963-61-0 431963-62-1 431963-63-2 431963-64-3
431963-65-4 431963-66-5 431963-67-6 431963-68-7 431963-69-8
431963-70-1 431963-71-2 431963-72-3 431963-73-4 431963-74-5

431963-75-6 431963-76-7 431963-77-8 431963-78-9 431963-79-0
 431963-80-3, 31: PN: WO0242441 SEQID: 7 unclaimed DNA 431963-81-4
 431963-82-5 431963-83-6 431963-84-7 431963-85-8 431963-86-9
 431963-87-0
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; purifn., cloning, characterization and
 therapeutic use of human von Willebrand factor-cleaving protease)
 IT 431965-66-1
 RL: PRP (Properties)
 (unclaimed sequence; purifn., cloning, characterization and
 therapeutic
 use of human von Willebrand factor-cleaving protease)
 IT 139691-92-2, Serine proteinase inhibitor
 RL: MSC (Miscellaneous)
 (von Willebrand factor-cleaving protease activity in presence of;
 purifn., cloning, characterization and therapeutic use of human von
 Willebrand factor-cleaving protease)

L6 ANSWER 10 OF 42 CAPLUS COPYRIGHT 2003 ACS
 AN 2002:736705 CAPLUS
 DN 137:268390
 TI Composition exhibiting a von Willebrand factor (**vWF**)
 protease activity comprising a polypeptide chain with the amino
 acid sequence AAGGILHLELLV
 IN Laemmle, Bernhard; Gerritsen, Helena Elisabeth; Furlan, Miha; Turecek,
 Peter; Schwarz, Hans-Peter; Scheifflinger, Friedrich; Antoine, Gerhard;
 Kerschbaumer, Randolph; Tagliavacca, Luigina; Zimmermann, Klaus
 PA Switz.
 SO U.S. Pat. Appl. Publ., 15 pp., Cont.-in-part of U.S. Ser. No. 721,254.
 CODEN: USXXCO
 DT Patent
 LA English
 IC ICM A61K038-48
 ICS C12N009-64
 NCL 424094630
 CC 63-3 (Pharmaceuticals)
 Section cross-reference(s): 1, 3
 FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 2002136713	A1	20020926	US 2001-833328	20010412
	WO 2002042441	A2	20020530	WO 2001-EP13391	20011120
	WO 2002042441	A3	20020808		
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,			
		CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,			
		HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,			
		LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,			
		RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,			
		VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,			
		CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,			
		BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	AU 2002018306	A5	20020603	AU 2002-18306	20011120
PRAI	US 2000-721254	A2	20001122		
	US 2001-833328	A	20010412		
	WO 2001-EP13391	W	20011120		
AB	The invention relates to vWF cleaving entities having a mol. wt. of 180 kD, 170 kD, 160 kD, 120 kD or 110 kD and an N-terminal amino acid sequence of AAGGILHLELLV, vWF cleaving complexes and methods for their prodn.				

ST vonWillebrand factor proteinase peptide sequence

IT Purpura (disease)
 (Henoch-Schoenlein's; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Anticoagulants
 Genetic mapping
 Genetic vectors
 Human
 Molecular cloning
 Molecular weight distribution
 Preeclampsia
 Protein sequences
 Thrombosis
 cDNA sequences
 (compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Antibodies
 Clusterin
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Kidney, disease
 (hemolytic-uremic syndrome; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Chromosome
 (human 9; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Platelet (blood)
 (thrombocytopenia, neonatal; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Embolism
 (thromboembolism; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT Purpura (disease)
 (thrombotic thrombocytopenic; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 462663-84-9
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (amino acid sequence; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 116614-45-0
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (calpain proteinase inhibitor; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 109319-16-6
 RL: BSU (Biological study, unclassified); REM (Removal or disposal); BIOL (Biological study); PROC (Process)

(compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 14127-61-8, Calcium ion, biological studies 22537-39-9, Strontium ion, biological studies 22541-12-4, Barium ion, biological studies 199128-68-2, Von Willebrand factor proteinase
 RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 37259-58-8, Serine proteinase 78990-62-2, Calpain
 RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (inhibitors; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 462663-85-0
 RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
 (nucleotide sequence; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 55-91-4, Diisopropyl fluorophosphate
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
 (serine proteinase inhibitor; compn. exhibiting von Willebrand factor protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 462674-97-1 462674-98-2
 RL: PRP (Properties)
 (unclaimed nucleotide sequence; compn. exhibiting von Willebrand factor (vWF) protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 462674-96-0 462693-10-3
 RL: PRP (Properties)
 (unclaimed protein sequence; compn. exhibiting von Willebrand factor (vWF) protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

IT 431079-93-5 431079-94-6 462647-98-9
 RL: PRP (Properties)
 (unclaimed sequence; compn. exhibiting von Willebrand factor (vWF) protease activity comprising polypeptide chain with amino acid sequence AAGGILHLELLV)

6 ANSWER 8 OF 42 CAPLUS COPYRIGHT 2003 ACS

AN 2002:849833 CAPLUS

DN 137:365556

TI Preparation of human Von willebrand factor (VWF) specific protease and the

uses of protease in therapeutics

IN Soejima, Kenji; Mimura, Noriko; Maeda, Hiroaki; Nozaki, Chikateru; Hamamoto, Takayoshi; Nakagaki, Tomohiro

PA Juridical Foundation the Chemo-Sero-Therapeutic Research Institute, Japan

SO PCT Int. Appl., 144 pp.

CODEN: PIXXD2

DT Patent

LA Japanese

IC ICM C12N015-57

ICS C12N009-50; C12P021-00; A01N067-027; C12N001-15; C12N001-19;
C12N001-21; C12N015-00; A61K038-46; A61P007-02; A61P043-00;
A61K045-00; A61K048-00; A61K031-711; G01N033-573; G01N033-573;
G01N033-15; G01N033-50

CC 7-2 (Enzymes)

Section cross-reference(s): 1, 3, 13

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2002088366	A1	20021107	WO 2002-JP4141	20020425
	W: AU, CA, CN, JP, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
PRAI	JP 2001-128342	A	20010425		
	JP 2001-227510	A	20010727		
	JP 2001-302977	A	20010928		
	JP 2002-17596	A	20020125		

AB This invention provides a process of prepn. and characterization of a protease specific to Von willebrand factor (VWF) purified from human.

The

protease exhibits catalytic activity of cleaving of VWF at position 842Tyr-843Met and mol. wt. 105-160 kDa and 160-250 kDa on SDS PAGE under reduced and oxidized conditions. Partial **VWF protease** internal sequence, Leu-Leu-Val-Ala-Val, and N-terminal sequence Ala-Ala-Gly-Gly-Ile-Leu-His-Leu-Glu-Leu-Leu-Val-Ala-Val were used for design primers for cloning of full length cDNA for VWF. The invention also provides cDNA and protein sequences of VWF specific protease and tissue distribution of the protease. The human VWF specific protease can be used for treatment liver disease such as thrombotic thrombocytopenic purpura.

ST cDNA protein sequence human Von willebrand factor **VWF protease**

IT Electrophoresis

(SDS-Page, for VWF specific protease assay; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT Liver, disease

(VWF specific protease assocd. with, treatment of; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT Human

(VWF specific protease from; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT Mouse

(VWF specific protease homolog from; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT Drugs
(VWF specific protease used as; prepn. of human Von willebrand factor
(VWF) specific protease and uses of protease in therapeutics)

IT cDNA sequences
(for VWF specific protease and fragment, of human and homolog of
mouse;
prepn. of human Von willebrand factor (VWF) specific protease and uses
of protease in therapeutics)

IT Gene, animal
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP
(Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(for VWF specific protease of human and sequence homolog of mouse;
prepn. of human Von willebrand factor (VWF) specific protease and uses
of protease in therapeutics)

IT Molecular cloning
(for VWF specific protease of human; prepn. of human Von willebrand
factor (VWF) specific protease and uses of protease in therapeutics)

IT Antisense oligonucleotides
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL
(Biological study); USES (Uses)
(for VWF specific protease; prepn. of human Von willebrand factor
(VWF)
specific protease and uses of protease in therapeutics)

IT Drug screening
(for identification of agonist and antagonist of protease; prepn. of
human Von willebrand factor (VWF) specific protease and uses of
protease in therapeutics)

IT Blood plasma
(fraction I paste, VWF specific protease isolated from; prepn. of
human
Von willebrand factor (VWF) specific protease and uses of protease in
therapeutics)

IT Peptides, biological studies
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL
(Biological study)
(fragment of VWF specific protease; prepn. of human Von willebrand
factor (VWF) specific protease and uses of protease in therapeutics)

IT Immunoassay
(immunoblotting, SDS-Page, for VWF specific protease assay; prepn. of
human Von willebrand factor (VWF) specific protease and uses of
protease in therapeutics)

IT Diagnosis
(mol., VWF specific protease used in; prepn. of human Von willebrand
factor (VWF) specific protease and uses of protease in therapeutics)

IT Protein sequences
(of VWF specific protease of human; prepn. of human Von willebrand
factor (VWF) specific protease and uses of protease in therapeutics)

IT Cell aggregation
(platelet, VWF specific protease assocd. with, treatment of; prepn. of
human Von willebrand factor (VWF) specific protease and uses of
protease in therapeutics)

IT Purpura (disease)
(thrombotic thrombocytopenic, VWF specific protease assocd. with,
treatment of; prepn. of human Von willebrand factor (VWF) specific
protease and uses of protease in therapeutics)

IT Antibodies
RL: ARG (Analytical reagent use); BSU (Biological study, unclassified);
DGN (Diagnostic use); THU (Therapeutic use); ANST (Analytical study);
BIOL
(Biological study); USES (Uses)

(to VWF specific protease; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT 475007-55-7, Protease (human VWF specific fragment 1) 475007-58-0, Protease (human VWF specific) 475007-59-1 475007-60-4 475007-61-5 475007-62-6 475007-63-7

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(amino acid sequence; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT 475007-53-5 475007-54-6 475007-56-8 475007-57-9 475007-64-8, DNA (human VWF specific protease cDNA) 475007-65-9 475007-66-0 475007-67-1 475007-68-2 475007-69-3 475007-70-6 475007-71-7 475007-72-8

RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)

(nucleotide sequence; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT 9001-92-7, Protease

RL: BSU (Biological study, unclassified); DGN (Diagnostic use); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (of human and homolog of mouse, protease; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT 109319-16-6

RL: BSU (Biological study, unclassified); BIOL (Biological study) (specific, protease; prepn. of human Von willebrand factor (VWF) specific protease and uses of protease in therapeutics)

IT 475029-48-2 475029-49-3 475029-50-6 475029-51-7 475029-52-8 475029-53-9 475029-54-0 475029-55-1 475029-56-2 475029-57-3 475029-58-4 475029-59-5 475029-60-8 475029-61-9 475029-62-0 475029-63-1 475029-65-3 475029-66-4 475029-67-5 475029-68-6 475029-69-7 475029-70-0 475029-71-1 475029-72-2 475029-73-3

RL: PRP (Properties)

(unclaimed nucleotide sequence; prepn. of human Von willebrand factor (VWF) specific protease and the uses of protease in therapeutics)

IT 475029-64-2

RL: PRP (Properties)

(unclaimed protein sequence; prepn. of human Von willebrand factor (VWF) specific protease and the uses of protease in therapeutics)

IT 98849-88-8 474938-84-6 474938-85-7 474938-86-8 474938-87-9

RL: PRP (Properties)

(unclaimed sequence; prepn. of human Von willebrand factor (VWF) specific protease and the uses of protease in therapeutics)

RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD

- RE
- (1) Furlan, M; Blood 1998, V91(8), P2839 CAPLUS
 - (2) Immuno Ag; JP 2000508918 A 2000
 - (3) Immuno Ag; WO 9741206 A3 2000 CAPLUS

L8 ANSWER 1 OF 3 USPATFULL
 AN 2002:250775 USPATFULL
 TI Composition exhibiting a von willebrand factor (vWF)
 protease activity comprising a polypeptide chain with the amino
 acid sequence AAGGILHLELLV
 IN Laemmle, Bernhard, Bolligen, SWITZERLAND
 Gerritsen, Helena Elisabeth, Boswil, SWITZERLAND
 Furlan, Miha, Bern, SWITZERLAND
 Turecek, Peter, Klosterneuburg, AUSTRIA
 Schwarz, Hans-Peter, Vienna, AUSTRIA
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 Kerschbaumer, Randolph, Vienna, AUSTRIA
 Tagliavacca, Luigina, UNITED STATES
 Zimmermann, Klaus, Vienna, AUSTRIA
 PI US 2002136713 A1 20020926
 AI US 2001-833328 A1 20010412 (9)
 RLI Continuation-in-part of Ser. No. US 2000-721254, filed on 22 Nov 2000,
 PENDING
 DT Utility
 FS APPLICATION
 LREP Baxter Healthcare Corporation, P.O. Box 15210, Irvine, CA, 92614
 CLMN Number of Claims: 35
 ECL Exemplary Claim: 1
 DRWN 5 Drawing Page(s)
 LN.CNT 909
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 2 OF 3 USPATFULL
 AN 2000:67429 USPATFULL
 TI Purified multimerase
 IN Furlan, Miha, Bern, Switzerland
 Laemmle, Bernhard, Bollingen, Switzerland
 Schwarz, Hans Peter, Vienna, Austria
 Turecek, Peter, Klosterneuburg Weidling, Austria
 Eibl, Johann, Vienna, Austria
 PA Baxter Aktiengesellschaft, Vienna, Austria (non-U.S. corporation)
 PI US 6068838 20000530
 AI US 1996-656589 19960531 (8)
 PRAI AT 1996-769 19960429
 AT 1996-770 19960429
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Eisenchenk, Chris; Assistant Examiner: Zeman, Mary K
 LREP Foley & Lardner
 CLMN Number of Claims: 32
 ECL Exemplary Claim: 1
 DRWN 18 Drawing Figure(s); 18 Drawing Page(s)
 LN.CNT 1128
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L8 ANSWER 3 OF 3 PATOSWO COPYRIGHT 2003 WILA
 AN 2002:787013 PATOSWO ED 20020606 EW 200222 FS OS
 TI VON WILLEBRAND FACTOR (vWF) CLEAVING PROTEASE POLYPEPTIDE, NUCLEIC ACID
 ENCODING THE POLYPEPTIDE AND USE OF POLYPEPTIDE.
 IN LAEMMLE, Bernhard, Schuetzenweg 3, CH-3065 Bolligen, CH;
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 SCHEIFLINGER, Friedrich, Michelbeuerngasse 4/17, A-1090 Vienna, AT (only US);
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 VOELKEL, Dirk, Podhagskygasse 2/17, A-1220 Vienna, AT (only US)
 Wila-IPA-2002-H22-T1
 Patent
 Application in English
 W AE; W AG; W AL; W AM; W AT; W AU; W AZ; W BA; W BB; W BG; W BR; W BY; W BZ; W CA; W CH; W CN; W CO; W CR; W CU; W CZ; W DE; W DK; W DM; W DZ; W EE; W ES; W FI; W GB; W GD; W GE; W GH; W GM; W HR; W HU; W ID; W IL; W IN; W IS; W JP; W KE; W KG; W KP; W KR; W KZ; W LC; W LK; W LR; W LS; W LT; W LU; W LV; W MA; W MD; W MG; W MK; W MN; W MW; W MX; W MZ; W NO; W NZ; W PL; W PT; W RO; W RU; W SD; W SE; W SG; W SI; W SK; W SL; W TJ; W TM; W TR; W TT; W TZ; W UA; W UG; W US; W UZ; W VN; W YU; W ZA; W ZW;
 RW AT; RW BE; RW CH; RW CY; RW DE; RW DK; RW ES; RW FI; RW FR; RW GB; RW GR; RW IE; RW IT; RW LU; RW MC; RW NL; RW PT; RW SE; RW TR; RW AM; RW AZ; RW BY; RW KG; RW KZ; RW MD; RW RU; RW TJ; RW TM; RW GH; RW GM; RW KE; RW LS; RW MW; RW MZ; RW SD; RW SL; RW SZ; RW TZ; RW UG; RW ZM; RW ZW; RW BF; RW BJ; RW CF; RW CG; RW CI; RW CM; RW GA; RW GN; RW GQ; RW GW; RW ML; RW MR; RW NE; RW SN; RW TD; RW TG
 WOA2 PCT-PUBLICATION
 WO 2002042441 A2 20020530
 20020530
 WO 2001-EP13391 20011120
 US 2000-721254 20001122
 US 2001-833328 20010412